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(71) Applicant (for all designated States except US): **FIRST HORIZON PHARMACEUTICAL CORPORATION**  
[US/US]; 660 Hembree Parkway, Suite 106, Roswell, GA 30076 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **VENKATARAMAN, Balaji** [IN/US]; 1214 Rosemount Parkway, Roswell, GA 30076 (US).

(74) Agents: **HUSEMAN, Cheryl, L. et al.; Jones & Askew, LLP**, 2400 Monarch Tower, 3424 Peachtree Road, N.E., Atlanta, GA 30326 (US).

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(54) Title: **METHODS OF ADMINISTRATION OF GLYCOPYRROLATE COMPOSITIONS**

(57) Abstract: The present invention comprises methods and compositions for the treatment of various conditions that interfere with patients' lifestyles, lead to social isolation, and involve pain and debilitation. Methods are provided for the treatment of conditions such as Frey's Syndrome, gustatory sweating, hyperhidrosis, sialorrhea, myasthenia gravis and Meniere's Disease. Preferably, these conditions are treated with methods of administration of compositions of glycopyrrolates. The present invention comprises methods of administration of glycopyrrolate compositions comprising injectable and noninvasive routes for drug delivery, including but not limited to, the oral, nasal, pulmonary, rectal, buccal, vaginal, transdermal and ocular routes.

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## METHODS OF ADMINISTRATION OF GLYCOPYRROLATE COMPOSITIONS

### Cross-Reference to Related Application

5            This application claims benefit of the pending  
prior U.S. Provisional Application 60/146,823 filed on  
August 2, 1999.

## Technical Field

10                   The present invention is directed to methods of administration of compositions to treat specific conditions. More specifically, the present invention is directed to treatment of conditions with the administration of glycopyrrolate compositions.

## Background of the Invention

There are several conditions or pathologies having mild to severe symptoms that can limit a patient's lifestyle and limit a patient's interactions with other persons. In particular, such pathologies include gustatory sweating and Frey's Syndrome, sialorrhea, hyperhidrosis, Meniere's Disease and myasthenia gravis. Though various treatment regimens and administrations of pharmaceuticals have been tried, none of these have provided relief to those exhibiting these pathologies. One compound that has been used for treatment is glycopyrrolate.

Glycopyrrolate (3-[cyclopentylhydroxyphenylacetyl)oxyl]-1,1-dimethylpyrrolidinium bromide), is a quaternary ammonium compound that is a polar molecule that will not easily cross lipid membranes. Glycopyrrolate is an antimuscarinic agent and acts as an antagonist for cholinergic drugs such as anticholinesterases. Antimuscarinics are known to act on structures that are innervated by postganglionic cholinergic nerves. Such structures so innervated include smooth muscle, cardiac muscle, exocrine glands and autonomic ganglia. For more complete description, see Merck Index, 11<sup>th</sup> Edition, and

the Physician's Desk reference, 1998 (A.H. Robbins, Robinul® and Robinul Forte), both of which are incorporated herein in their entirety.

5 Glycopyrrolate has been used as an adjunct therapy for peptic ulcer treatment. Injectable forms of glycopyrrolate have been used as a preoperative antimuscarinic to reduce gastric and mucosal secretions, and to inhibit cardiac vagal inhibitory reflexes. These uses of glycopyrrolate, as aids in surgery, are possible with injectable doses. In this setting, glycopyrrolate is always used in combination with other  
10 sedative or hypnotic agents and only in a single administration.

As noted in Mirakhur et al, Anaesthesia, 1983, 38:1195-1204, it is believed that oral absorption of glycopyrrolate is poor and erratic and that an oral dose must be  
15 35 times greater than a parenteral dose. Absorption studies also show this effect. After intravenous administration of radioactive glycopyrrolate, peak radioactivity was found in all organs in 5-10 minutes except for the brain. Liver, kidney and intestines showed traces of radioactivity at 24 hours. After oral  
20 administration, stomach and intestine showed maximum amount of radioactivity and absorption from the gastrointestinal tract was poor. See Mirakhur, above.

A routine intramuscular premedicant dose of glycopyrrolate is 0.2-0.4 mg in an adult and approximately 10  
25 µg/kg for children. For intravenous administration, especially where there is a need for protection against bradycardia, the adult dose is 0.2 mg, or on a weight related basis, 4-5 µg/kg, and 5-10 µg/kg in children.

Another use for glycopyrrolate is treatment of  
30 gustatory sweating and Frey's Syndrome. Frey's Syndrome presents with localized facial sweating and flushing during mastication. Frey's Syndrome arises after trauma or surgery to the face or neck, particularly in the parotid gland area. Gustatory sweating has similar symptoms but is usually caused  
35 by conditions other than surgery to the facial region, such as a

result of diabetes mellitus causing diabetic neuropathy or nephropathy. Generally, the syndrome is not a cause of major morbidity, though if the condition is severe, it can disturb eating patterns and occasionally interfere with control of glucose levels in diabetics. For most persons, the condition is troublesome and embarrassing. The sweating and flushing is activated by the stimulation of the salivary glands and usually results in the areas innervated by the auriculotemporal nerve, though the sweating can occur circumorally and in the scalp.

The areas affected by gustatory sweating can be determined using the minor starch-iodine test. The test is conducted by painting the affected and surrounding areas of skin with a solution containing 3 g of iodine, 20 g of castor oil and enough absolute alcohol to make a final solution of 200 g. The area is allowed to dry and then dusted lightly with a finely powered cornstarch. The person then chews a slice of lemon for 3 to 5 minutes. The starch powder will turn blue-black in the presence of iodine and moisture.

There are a variety of treatments for Frey's Syndrome or gustatory sweating, though none currently in use are satisfactory. A common treatment for gustatory sweating is to use a roll-on cream containing glycopyrrolate at a 1-2% concentration. The use of creams or roll-on treatments on the face, neck or in the hair are often messy, undesirable to patients and cause reactions with the skin. The creams must be applied and then allowed to dry. Scalp treatment cannot be achieved with this administrative route. Patients would prefer the simple step of taking oral medications. Oral anticholinergics such as propantheline and oxybutynin, and alpha 2 blocker clonidine have all been reported to be effective in treating gustatory sweating. These drugs have many undesirable side effects that limit or prevent their use.

Another condition that has been treated using glycopyrrolate is sialorrhea, or drooling, which is the unintentional loss of saliva and other oral contents from the

mouth. Persistent drooling beyond the ages of 3 or 4 years is considered abnormal drooling. Such drooling may be found in individuals with neurological dysfunction such as motor deficits, e.g., cerebral palsy, peripheral neuromuscular disease, facial paralysis, and severe mental retardation, and other conditions such as esophageal cancer. For example, socially significant drooling occurs in approximately 10% of patients with cerebral palsy. Drooling causes impairment of speech, feeding and swallowing problems, upper respiratory congestion and aspiration. Control of drooling is important in preventing choking and gagging in persons with posterior drooling.

Persons who are motor-impaired can use the many new electronic assistance aids to communicate, navigate and provide more integration and self-sufficiency in everyday life. Unfortunately for those who drool, many of the aids are controlled through the mouth or facial manipulations. The drooling may cause social isolation and inability to use the new devices.

Not only is the drooling annoying and limiting for the person with sialorrhea, there are problems for the caregivers. Caregivers must clean and control the drooling, and remove the drool from the body, clothes and surrounding equipment of the drooler. Additionally, caregivers must be very careful about exposure to bodily fluids such as drool. Hepatitis B is a commonly transmitted virus among those who are exposed to oral bodily secretions.

The combination of drooling and lack of motor skills, or difficulty in swallowing, speaking and breathing, makes treatment of drooling difficult. Treatments for drooling include positioning techniques, oral sensorimotor therapies, prostheses, surgical procedures to eliminate drooling, medications, and radiation. None of these treatments provide the relief sought by the patients without side effects. Anticholinergic drugs have been used as treatment for drooling, the side effects from such drugs create additional

problems for the patients and caregivers. The side effects include restlessness, overactivity, irritability, listlessness, drowsiness, automatisms, staring, insomnia, facial flushing, dry mouth, vomiting, abdominal pain and trouble with urinary voiding. These side effects are particularly unwanted in patients who are wheelchair bound or who have trouble controlling muscular movements in general.

Glycopyrrolate, in an oral form, was used in a study of control of drooling in children with cerebral palsy. See Blasco, et al., Arch. Pediatr. Adolesc. Med. 1996;150:932-935. The most effective dose was 0.01 to 0.82 mg/kg per day, for a total daily dose of 1-8 mg. Though the glycopyrrolate reduced the drooling, the side effects often led to discontinuation of drug therapy. Another study reported that the recommended intravenous dose of glycopyrrolate to control drooling was 0.004 to 0.01 mg/kg/dose, every 3-4 hours, and the recommended oral dose is at least 10 times the intravenous dose, 0.04 to 0.1 mg/kg/dose, 3 to 4 times a day. See Bachrach et al., Clin. Pediatr. 1998; 37:485-490. Glycopyrrolate, in an injectable formulation, was used to treat excessive secretions in patients that had esophageal cancer. The dose was 0.2 mg every 6 hours by gastrostomy tube or nebulization. The gastrointestinal or lung absorption of the glycopyrrolate solution was slow and erratic. See Rashid et al., Annals of Oncology, 1997, 8:198-199.

Another condition that may cause social isolation in patients is hyperhidrosis, excessive sweating of plantar and palmar surfaces, the palms of the hands and the soles of the feet. The medical treatment of hyperhidrosis is usually ineffective in all but the mildest cases, and it is currently taught that anticholinergic compounds have little effect when used directly on palms and soles and side effects of these drugs preclude oral use. A somewhat successful treatment has been to use direct current iontophoresis, employing a solution of glycopyrronium bromide or hexopyrronium bromide in water.

See Abell, et al., Brit. J. Derm. 1974; 91:87-91. Using a 0.1% solution of glycopyrrolate in water, the palm or sole is placed in an iontophoresis apparatus and current is applied and increased until pain is experienced and maintained there for 15 minutes. Such treatments were continued twice weekly or once a week, if possible, to reduce hyperhidrosis. Of the 27 persons in the study, all relapsed when treatment stopped, though 5 remained symptom free for 8 weeks after treatment stopped. Such treatments are not very effective in treating hyperhidrosis.

Iontophoresis is the electrically driven application of drugs or medicants, in their ionic form, to the surface tissues of a patient. The application of electric current causes migration of ions into the tissue wherein such migration is proportional to the quantity of current applied through the iontophoretic system. One of the major drawbacks of iontophoresis is skin irritation or burns which can occur due to high current levels. It is known that the impedance of a patient's skin can range from over 100,000 ohms to nearly 1,000 ohms, depending on the duration that the iontophoretic current is applied, the magnitude of the current which is being delivered, the location of the system on the patient's body, and other factors. In a system where the desired current level, which is determined in part by the drug administered to the patient, is 1 milliamp, a voltage potential of 100 volts would result if the skin impedance is 100,000 ohms. Such a voltage would cause undesirable sensations to the user.

A condition that can severely limit the lifestyle of a sufferer with the condition is Meniere's Disease. Meniere's Disease is characterized by recurrent episodes of vertigo associated with nausea and vomiting. Between the episodes, the patients exhibit low-frequency sensorineural hearing loss and tinnitus, usually in one ear. Additionally, Meniere's Disease is characterized by a sensation of fullness in the affected ear.

Current therapy for Meniere's Disease includes diet and medication. A low sodium diet and a diuretic have been shown to reduce the number and severity of the vertigo episodes. There has been only one published study that evaluates the use of glycopyrrolate in the treatment of vertigo associated with Meniere's Disease. See Storper, 1998, The Laryngoscope, 108:1442-1445. All of the subjects of this study were on a low sodium diet and were concurrently taking a diuretic. The experimental subjects received tablets containing 2 mg of glycopyrrolate to be taken twice daily, and almost all saw a reduction in number and severity of vertigo attacks. Myasthenia gravis is a disease characterized by episodic weakness, chiefly in muscles innervated by cranial nerves, and generally improved by cholinesterase-inhibiting drugs. The disease is caused by an autoimmune reaction that effects the acetylcholine receptors of the postsynaptic neuromuscular junction. This causes the loss dysfunction of the acetylcholine receptors and interferes with normal neuromuscular transmission. Treatments include administration of anticholinesterases and plasmaphoresis to treat symptoms and other therapies, such as steroids, immunosuppressive and thymectomy alter the immune status to prevent further deterioration of the acetylcholine receptors.

Administration of glycopyrrolate for treatment of myasthenia gravis is contraindicated according to the PDR and the maker of Robinul, A.H. Robbins. It was reported in 1981 that two patients with myasthenia gravis were administered glycopyrrolate. See South African Medical Journal, 24 October 1981. There is no teaching of any relief of symptoms of myasthenia gravis, merely that 1 mg given two or three times daily relieved the patients' symptoms of epigastric discomfort and other gastrointestinal symptoms. The reference suggests that glycopyrrolate was a substitute for atropine treatment.



The conditions described herein have varied symptoms, all of which are limiting to the patient's lifestyle and social interactions. Though there have been some treatments of these symptoms, none have provided compositions that provide ease of administration with few side effects and effective treatment. What is needed are easily tolerated, efficacious methods of treating these conditions. What is particularly needed are methods of treatment of gustatory sweating. Such methods could treat symptoms on the face, neck and scalp without the need for application of creams and lotions to the skin and hair.

What is also needed are compositions and methods of treatment for drooling that are easily used by those who drool and easily administered by the caregivers. Methods are needed that provide efficient and easy administration of effective compounds for protecting and assisting caregivers and providing relief for droolers.

Simple methods of treating hyperhidrosis are needed that are long lasting and effective. Preferably, such methods provide administration of compositions that can be administered orally or topically.

What is further needed are methods of treatment of Meniere's Disease that are easily tolerated and provide relief. Additionally, methods of treatment for myasthenia gravis are needed. It would be most beneficial to have methods of administration that include topical, transdermal or modified oral treatments.

What is further needed are methods of treating pathologies that include delivery of effective compositions that provide for delivery of the active agent that avoids a first pass through the liver, and thus lowers the metabolic breakdown of the composition.

### Summary of the Invention

5           The present invention comprises methods and compositions for the treatment of various conditions that have symptoms that, in mild cases interfere with patients' lifestyles and lead to social isolation, and in severe cases, lead to pain and debilitation. Methods are provided for the treatment of conditions such as Frey's Syndrome, gustatory sweating, hyperhidrosis, sialorrhea, myasthenia gravis and Meniere's Disease. Preferably, these conditions are treated with methods of administration of compositions of glycopyrrolates.

10           The present invention comprises methods of administration of glycopyrrolate compositions comprising injectable and noninvasive routes for drug delivery, including but not limited to, the oral, nasal, pulmonary, rectal, buccal, vaginal, transdermal and ocular routes. Glycopyrrolate may be administered through these routes of administration in compositions that allow for sustained release, controlled release or time-release dosing to the patient. The release profile of the compositions of the present invention allow for greater safety in administration of glycopyrrolates and result in fewer side effects for patients.

20           It is an object of the present invention to provide dosage forms and methods for administering compositions that are easily administered to persons having Frey's Syndrome or gustatory sweating.

25           It is also an object of the invention to provide dosage forms and methods for administering compositions that promote high patient acceptance and compliance in persons having Frey's Syndrome or gustatory sweating.

30           It is another object of the invention to provide dosage forms and methods for administering compositions that maximize drug absorption in persons having Frey's Syndrome or gustatory sweating.

It is an object of the present invention to provide dosage forms and methods for administering compositions that are easily administered to persons having hyperhidrosis.

5 It is also an object of the invention to provide dosage forms and methods for administering compositions that promote high patient acceptance and compliance in persons having hyperhidrosis.

10 It is another object of the invention to provide dosage forms and methods for administering compositions that maximize drug absorption in persons having hyperhidrosis.

It is an object of the present invention to provide dosage forms and methods for administering compositions that are easily administered to persons having Meniere's Disease.

15 It is also an object of the invention to provide dosage forms and methods for administering compositions that promote high patient acceptance and compliance in persons having Meniere's Disease.

20 It is another object of the invention to provide dosage forms and methods for administering compositions that maximize drug absorption in persons having Meniere's Disease.

It is an object of the present invention to provide dosage forms and methods for administering compositions that are easily administered to persons having sialorrhea.

25 It is also an object of the invention to provide dosage forms and methods for administering compositions that promote high patient acceptance and compliance in persons having sialorrhea.

30 It is another object of the invention to provide dosage forms and methods for administering compositions that maximize drug absorption in persons having sialorrhea.

It is an object of the present invention to provide dosage forms and methods for administering compositions that are easily administered to persons having myasthenia gravis.

It is also an object of the invention to provide dosage forms and methods for administering compositions that promote high patient acceptance and compliance in persons having myasthenia gravis.

5 It is another object of the invention to provide dosage forms and methods for administering compositions that maximize drug absorption in persons having myasthenia gravis.

10 These and other objects are accomplished by providing methods of routes of administration of compositions comprising glycopyrrolate.

The glycopyrrolate may be delivered via embodiments such as a device of determined physical form, such as a tablet, patch, or troche, or in free form, such as a gel, ointment, cream, or gum. The drug delivery vehicles can include oral, nasal, injectable, or transdermal methods of administration.

20 These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments and the appended claims.

### Detailed Description

25 The present invention is directed to methods and compositions for treatment of certain conditions. These conditions include, but are not limited to, Frey's Syndrome, gustatory sweating, Meniere's disease, hyperhidrosis, sialorrhea and myasthenia gravis. Preferred methods of treatment include the administration of compositions comprising glycopyrrolate in an effective amount to treat symptoms of these conditions. The methods of the present invention comprise routes of administration that include, but are not limited to, oral, buccal, nasal, transdermal, injectable, slow release, controlled release, iontophoresis, sonophoresis, and other delivery devices and methods. Injectable methods

30  
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include, but are not limited to, parenteral routes of administration, intravenous, intramuscular, subcutaneous, intraperitoneal, intraspinal, intrathecal, intracerebroventricular, intraarterial and other routes of injection.

5           These inventions contemplate compositions that provide controlled, slow release, or sustained release of the therapeutic compound over a predetermined period of time. Administration of the glycopyrrolate composition using these formulations allows for a desired concentration of the  
10           compound to be maintained in the bloodstream of the patient for a longer period of time than with conventional formulations. Slow release, controlled or sustained release formulations are known to those skilled in the art and include formulations such as coated tablets, pellets, capsules,  
15           dispersion of the active agent in a medium that is insoluble in physiologic fluids or where the release of the active agent is released after degradation of the formulation due to mechanical, chemical or enzymatic activity.

          It is to be understood that this invention is not  
20           limited to the particular formulations, process steps, and materials disclosed herein as such formulations, process steps, and materials may vary somewhat. It is also to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to  
25           be limiting since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

          It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates  
30           otherwise. Thus, for example, reference to a bilayer tablet containing "a glycopyrrolate composition" may include a mixture of such compositions, reference to "an adhesive" includes reference to one or more of such adhesives, and reference to "a bile salt" includes reference to a mixture of two  
35           or more of such bile salts.

As used herein, "chemical enhancer," "penetration enhancer", "permeation enhancer," and the like shall be inclusive of all enhancers that increase the flux of a permeant, drug, or other molecule across the mucosa and is limited only by functionality. In other words, all cell envelope disordering compounds, solvents, steroidal detergents, bile salts, chelators, surfactants, non-surfactants, fatty acids, and any other chemical enhancement agents are intended to be included.

Permeation enhancers are comprised of two primary categories of components, i.e., cell-envelope disordering compounds and solvents or binary systems containing both cell-envelope disordering compounds and solvents. As discussed above, other categories of permeation enhancer are known, however, such as steroidal detergents, bile salts, chelators, surfactants, non-surfactants, and fatty acids.

Cell envelope disordering compounds are known in the art as being useful in topical pharmaceutical preparations and function also in drug delivery through the skin or mucosa. These compounds are thought to assist in dermal penetration by disordering the lipid structure of the stratum corneum cell-envelopes. A list of such compounds is described in European Patent Application 43,738, published on Jun. 13, 1982, which is incorporated herein by reference. It is believed that any cell envelope disordering compound is useful for purposes of this invention.

Suitable solvents include water; diols, such as propylene glycol and glycerol; mono-alcohols, such as ethanol, propanol, and higher alcohols; DMSO; dimethylformamide; N,N-dimethylacetamide; 2-pyrrolidone; N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted alkyl-azacycloalkyl-2-ones (azonones) and the like.

As used herein, "bile salts" means steroidal detergents that are the natural or synthetic salts of cholanolic acid, e.g. the salts of cholic and deoxycholic acid or

combinations of such salts, and the unionized acid form is also included. Bile salt analogs having the same physical characteristics and that also function as permeation enhancers are also included in this definition.

5           As used herein, "transmucosal," "transbuccal," and similar terms mean passage of a glycopyrrolate composition into and through the mucosa to achieve effective therapeutic blood levels or deep tissue levels.

10           As used herein, "effective amount" means an amount of a glycopyrrolate composition that is sufficient to provide a selected effect and performance at a reasonable benefit/risk ratio attending any medical treatment. An effective amount of a permeation enhancer, as used herein, means an amount selected so as to provide the selected increase in  
15 permeability and, correspondingly, the desired depth of penetration, rate of administration, and amount of drug delivered.

          As used herein, "adhesive," "adhesive polymer", "mucoadhesive", or such similar terms refers to hydrophilic  
20 polymers, natural or synthetic, which, by the hydrophilic designation, can be either water soluble or swellable and which are compatible with the enhancers and glycopyrrolate compositions. Such adhesives function for adhering the dosage forms to the mucous tissues of the oral cavity, such as the  
25 gingiva. Such adhesives are inclusive of hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxy ethylcellulose, ethylcellulose, carboxymethyl cellulose, dextran, guar gum, polyvinyl pyrrolidone, pectins, starches, gelatin, casein, acrylic acid polymers, polymers of acrylic acid  
30 esters, acrylic acid copolymers, vinyl polymers, vinyl copolymers, polymers of vinyl alcohols, alkoxy polymers, polyethylene oxide polymers, polyethers, and mixtures thereof and the like.

          By "system", "drug delivery system",  
35 "transmucosal delivery system" or the like is meant a unit

dosage form of a drug composition, preferably glycopyrrolate compositions, including carriers, enhancers, and other components, in which the glycopyrrolate composition is contained in or accompanied by means for maintaining the drug composition in a drug transferring relationship or providing the glycopyrrolate compositions to the desired site in the body. Such means can be either a patch, tablet, troche, or other device of determined physical form for continuous drug administration thereto for systemic transport, or such means can be formulated in free form to be applied directly to the patient as a cream, gel, gum, ointment and the like. The term "troche" includes pastille, lozenge, morsulus, rotula, trochiscus, and the like. "Free form" means that the formulation is spreadable or malleable into a selected shape at the time of application. "Determined physical form" means that the formulation has a form determined by a device. The means used may be a device such as a tablet or matrix or liquid reservoir patch. A matrix patch contains the drug, permeation enhancer, and other optional ingredients suspended or dispersed in an adhesive layer. A reservoir patch contains the drug, permeation enhancer, and other optional ingredients in a reservoir, which can be in liquid form, or the liquid can be gelled or thickened by an agent such as mineral oil, petroleum jelly and various aqueous gelling agents and hydrophilic polymers. Such a reservoir or matrix patch is brought into contact with the surface and is held in place by a suitable adhesive. In a reservoir patch, the drug composition is applied to the surface through a permeable membrane forming the reservoir floor that is in direct contact with the surface.

The method of application of the present invention can vary within limits, but necessarily involves providing the selected glycopyrrolate compositions to the patient such that drug delivery is initiated and continues for a period of time sufficient to provide the selected pharmacological or biological response.



5 The compositions of the present invention preferably comprise glycopyrrolate, or glycopyrronium bromide. The present invention also contemplates and comprises the use of other forms of glycopyrronium associated with other ionic components, such as other salts of glycopyrronium. In addition, the compositions of the present invention comprise delivery vehicles or permeation enhancers known to those skilled in the art.

10 The compositions for treating the pathologies treated by the present invention can further include a pharmaceutically acceptable carrier. The compositions can also include other medicinal agents, pharmaceutical agents, carriers, adjuvants diluents and other pharmaceutical preparations known to those skilled in the art. These agents are  
15 known to those skilled in the art and are generally described as being biologically inactive and can be administered to patients without causing deleterious interactions with the active agent. Examples of carriers or excipients for oral administration include corn starch, lactose, magnesium stearate,  
20 microcrystalline cellulose and stearic acid, povidone, dibasic calcium phosphate and sodium starch glycolate. Any carrier suitable for the desired administration route is contemplated by the present invention.

25 Preferred methods of administration include oral routes. The compositions of the present invention can be contained in a gelatin capsule, tablet, liquid or powder, and such items may be coated for ease of swallowing. For oral administration, fine powders or granules may contain diluting, dispersing, and or surface active agents and may be present in  
30 water or in a syrup, in capsules or sachets in the dry state, or in a nonaqueous solution or suspension wherein suspending agents may be included, in tablets wherein binders and lubricants may be included or in a suspension in water or a syrup. Components that may be added such as flavoring,  
35 preserving, suspending, thickening or emulsifying agents.

Such preparations are known or apparent to those skilled in the art.

One embodiment of the present invention comprises methods of treatment of Frey's Syndrome, gustatory sweating, hyperhidrosis, Meniere's Disease and myasthenia gravis comprising administration of glycopyrrolate compositions through oral delivery compositions and devices. Oral delivery methods are often limited by chemical and physical barriers imposed by the body, such as the varying pH in the gastrointestinal tract, exposure to enzymes and the impermeability of the gastrointestinal membranes. Methods of the present invention for orally administering glycopyrrolate compositions may also include the coadministration of adjuvants with the compositions of the present invention. For example, resorcinols and nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecyl polyethylene ether, can be administered with or incorporated into the compositions of the present invention to artificially increase the permeability of the intestinal walls. Other methods include the coadministration of enzymatic inhibitors with the compositions of the present invention. Liposomes and emulsions are also contemplated in the present invention for delivery of the compositions.

Simple drug delivery systems of the present invention comprise capsules containing differently coated pellets of the drug. On release from the capsule, the uncoated pellets provide an initial amount of the glycopyrrolate composition to the body, and the coated pellets provide the glycopyrrolate composition over a period of time. Another system comprises a tablet made from a polymer containing the glycopyrrolate composition dispersed within. As the polymer slowly degrades in the stomach, the glycopyrrolate composition is released. Additional drug delivery systems include hydrogel materials with coated pills embedded in the hydrogel, such as that taught in U.S. Patent No. 4,659,558.

The unswollen hydrogel is swallowed and in the presence of fluids in the stomach, swells so that the hydrogel is retained within the stomach. The coated pills are released as the hydrogel degrades.

5           The present invention comprises methods of administering glycopyrrolate compositions for treatment of Frey's Syndrome, gustatory sweating, Meniere's Disease, hyperhidrosis, sialorrhea, and myasthenia gravis. The dosage of the glycopyrrolate composition administered will depend on  
10           the condition being treated, the particular composition, and other clinical factors such as weight and condition of the human and the route of administration of the composition. For administration to humans, a dosage of between approximately 0.001 to 300 mg/kg/day, preferably between approximately  
15           0.0005 and 50 mg/kg/day, and most preferably between approximately 0.001 to 10 mg/kg/day, is generally sufficient.

          The compositions of the present invention preferably comprise glycopyrrolate and more preferably comprise glycopyrrolate in a pharmaceutical composition. One  
20           of the agents that can be included in the pharmaceutical composition is a permeation enhancer. A permeation enhancer allows for more penetration of the active agent, glycopyrrolate, through the mucous membranes of the body. Permeation enhancers may also be incorporated in transdermal delivery  
25           systems. A permeation enhancer is preferably a member selected from the group consisting of cell envelope disordering compounds, solvents, steroidal detergents, bile salts, chelators, surfactants, non-surfactants, fatty acids, and mixtures thereof. A preferred organic solvent is a member selected from the  
30           group consisting of a C<sub>1</sub> or C<sub>3</sub> alcohol, and C<sub>3</sub> or C<sub>4</sub> diol, DMSO, DMA, DMF, 1-n-dodecylcyclazacyclo-heptan-2-one, N-methyl pyrrolidone, N-(2hydroxyethyl) pyrrolidone, triacetin, propylene carbonate and dimethyl isosorbide and mixtures thereof. A preferred cell-envelope disordering  
35           compound is a member selected from the group consisting of

isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monooleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and sorbitan esters and mixtures thereof. A preferred bile salt is a steroidal detergent selected from the group consisting of natural and synthetic salts of cholanic acid and mixtures thereof.

Another method of treatment of the present invention comprises administration of glycopyrrolate compositions using microspheres of artificial polymers or proteins that are used for delivery of compositions through various routes, such as gastrointestinal or nasal. Nasal delivery is considered an efficacious route of administration for treatment of Frey's Syndrome, gustatory sweating, Meniere's Disease, hyperhidrosis, sialorrhea and myasthenia gravis because the nose has a large surface area available for drug absorption due to the coverage of the epithelial surface by numerous microvilli and the subepithelial layer is highly vascularized. The venous blood from the nose passes directly into the systemic circulation and avoids the loss of drug in a first pass metabolism in the liver.

In order to enhance nasal delivery, absorption enhancers can be added to the compositions of the present invention. Bile salts or derivatives such as fusidic acid, or surfactants, especially nonionic surfactants, can be used to modify the properties of the nasal mucosa to enhance uptake. Microspheres can also be used, particularly those that swell in the presence of moisture. Albumin, starch and DEAE-Sephadex microspheres of 40-60  $\mu\text{m}$  in diameter have been used. These same absorption enhancers can be used in the present invention for enhanced absorption across other mucosal surfaces, such as the gastrointestinal tract or the oral cavity.

A preferred method of the present invention comprises treatment of Frey's Syndrome, gustatory sweating, Meniere's Disease, hyperhidrosis, sialorrhea and myasthenia

5 gravis by administration of glycopyrrolate compositions through the buccal and sublingual membranes. Both the buccal and sublingual membranes offer advantages over other routes of administration. For example, glycopyrrolate compositions administered through the buccal and sublingual routes have a rapid onset of action, reach high levels in the blood, avoid the first-pass effect of hepatic metabolism and avoid exposure of the glycopyrrolate compositions to fluids of the gastrointestinal tract. Additional advantages include easy access to the membrane sites so that the glycopyrrolate compositions can be applied, localized and removed easily. Further, there is good potential for prolonged delivery through the buccal membrane. Administration through the buccal mucosa may be better accepted than rectal dosing and generally avoids local toxic effects, such as has been a problem in nasal administration.

10 The sublingual mucosa includes the membrane of the ventral surface of the tongue and the floor of the mouth, whereas the buccal mucosa constitutes the lining of the cheek and lips. The sublingual mucosa is relatively permeable, thus giving rapid absorption and acceptable bioavailabilities of many drugs. Further the sublingual mucosa is convenient, easily accessible, and generally well accepted. This route has been a traditional route of administration of nitroglycerin and also buprenorphine and nifedipine. The sublingual mucosa is not well suited to sustained-delivery systems because it lacks an expanse of smooth and relatively immobile mucosa suitable for attachment of a retentive delivery system.

25 Solutes that facilitate the transport of solutes across biological membranes, known as penetration or permeation enhancers, are well known in the art for administering drugs. Such compositions are contemplated by the present invention as members of embodiments of the glycopyrrolate compositions, or may be administered simultaneously with, or before or after administration of

glycopyrrolate compositions. Penetration enhancers can be categorized as chelators, e.g., EDTA, citric acid, and salicylates; surfactants, such as sodium dodecyl sulfate (SDS); non-surfactants, e.g., unsaturated cyclic ureas; bile salts, e.g., sodium deoxycholate, sodium taurocholate; and fatty acids e.g., oleic acid, acylcarnitines, mono- and diglycerides.

Penetration enhancers are effective in facilitating mucosal drug administration. For an enhancer to work effectively, the enhancer and glycopyrrolate composition combination is held in position against mucosal tissues for a period of time sufficient to allow enhancer-assisted penetration of the glycopyrrolate composition across the mucosal membrane. In transdermal and transmucosal technology, this is often accomplished by means of a patch or other device that adheres to the skin layer by means of an adhesive.

Oral adhesives are well known in the art. These adhesives consist of a matrix of a hydrophilic, water soluble or swellable, polymer or mixture of polymers that can adhere to a wet mucous surface. These adhesives may be formulated as ointments, thin films, tablets, troches, and other forms. These adhesives may have had glycopyrrolate compositions mixed therewith to effectuate slow release or local delivery of a glycopyrrolate composition. Some have been formulated to permit absorption through the mucosa into the circulatory system of the individual.

The present invention comprises oral administration of glycopyrrolate compositions for the treatment of Frey's Syndrome, gustatory sweating, hyperhidrosis and myasthenia gravis. Oral administration includes, but is not limited to, administration through the mucosa of the mouth and any other surfaces of the alimentary canal, stomach, and the gastrointestinal tract.

The benefits of controlled release delivery systems for delivery of the compositions of the present invention are significant, and provide for reduction in the number of doses

and steady drug levels in the blood. One type of drug delivery system comprises using compositions that remain in the stomach over a prolonged period of time. The drug delivery system remains in the stomach and acts as an in vivo reservoir that releases drug at a controlled rate and continuously for absorption in the stomach or for passage to the intestines for absorption. Often the drug is administered from a delivery system that releases a drug as the system moves through the gastrointestinal tract over time. These systems eliminate the need for administering a number of single doses at periodic intervals. This system also provides the advantage of continuously supplying drugs so that the blood levels of the drug are controlled and remain at an optimum level.

In controlled release systems contemplated in the present invention, after oral ingestion, drugs are released by diffusion and erosion throughout the gastrointestinal tract to a significant degree. Methods of the present invention for the prolongation of gastric retention time, include incorporation of fatty acids to reduce physiological gastric emptying and the use of bioadhesive polymers. Such systems are known to those skilled in the art and comprise using polymers such as polycarbophyll, sodium carboxymethylcellulose, tragacanth gum, acrylates and methacrylates, modified celluloses and polysaccharide gums.

Another delivery system that is contemplated by the present invention for targeting drugs to the stomach while avoiding gastric emptying is known as a hydrodynamically balanced system. This system is based on capsules or tablets with bulk density lower than gastric fluid. Thus, the dosage form stays buoyant in the stomach. These dosage forms are comprised of 20-75% of one or more hydrocolloids, e.g., hydroxyethylcellulose and hydroxypropylmethylcellulose.

Other methods of delivery include gastroinflatable delivery devices. These devices contain one or several inflatable chambers that are filled with gas at body

temperature by a gasifying liquid or a gas-forming solid, such as bicarbonate or carbonate. The chambers are incorporated within a plastic matrix and the whole structure is encapsulated in gelatin. Dissolution of the gelatin coating inflates the device and drug diffusion occurs.

Other types of these devices include osmotic pressure compartments containing osmotically active salts. In the present invention, dissolution of these salts by the gastric fluid pumps out the glycopyrrolate composition. Others are based upon a floating bilayer compressed matrix. One of the layers is comprised of a hydrophilic polymer and a carbon dioxide generating composition. The carbon dioxide maintains buoyancy and the other hydrophilic layer releases the drug from the matrix. A further method for gastric drug targeting involves an intragastric retention shape, made of polyethylene or polyethylene blend.

The delivery systems described above may also be used in the present invention to target glycopyrrolate compositions to the upper small intestine. However targeting to other areas of the small intestine may involve several additional systems. The low stomach pH and presence of gastric enzymes have led to the development of enteric coating. This coating protects the gastric mucosa from drug irritation. Coating is done with a selectively insoluble substance, and protects drugs from inactivation by gastric enzymes and/or low pH.

The most common enteric coatings are methacrylic acid copolymers, cellulose acetate phthalate, cellulose acetate succinate, and styrol maleic acid copolymers. The most significant drawback of enteric coating is the variability in gastric emptying time. This results in a large variance in blood drug levels.

Another method of drug delivery in the small intestine comprises delivery systems that allow for drug absorption via the lymphatic system. Capillary and lymphatic



vessels are permeable to lipid-soluble compounds and low molecular weight moieties. Another approach for targeting drugs to the small intestine involves the use of intestinal sorption promoters. Such promoters include long chain fatty acids, including linoleic acid, acylcamitines, and palmitocarnitine.

Bioadhesives can also be used in the present invention to prolong intestinal transit, as in buccal delivery systems. The adhesion to the intestinal mucosa takes place either by mechanical interlocking or other mechanisms.

A preferred tablet for oral administration in the methods of the present invention, preferably for buccal delivery systems, comprises an adhesive layer comprising a hydrophilic polymer with one surface adapted to contact a first tissue of the oral cavity and adhere thereto when wet and an opposing surface in contact with and adhering to an adjacent drug/enhancer layer comprising a permeation enhancer and the glycopyrrolate composition. The drug/enhancer layer contacts and is in drug transfer relationship with the buccal mucosa when the adhesive layer contacts and adheres to the first tissue, preferably the gingiva. Preferably the hydrophilic polymer comprises compounds selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, ethylcellulose, carboxymethyl cellulose, dextran, guar-gum, polyvinyl pyrrolidone, pectins, starches, gelatin, casein, acrylic acid polymers, polymers of acrylic acid esters, acrylic acid copolymers, vinyl polymers, vinyl copolymers, polymers of vinyl alcohols, alkoxy polymers, polyethylene oxide polymers, polyethers, and mixtures thereof. The adhesive layer may additionally contain one or more members selected from the group consisting of fillers, tableting excipients, lubricants, flavors, and dyes and that the drug/enhancer layer additionally contain one or members selected from the group consisting of tableting excipients,

fillers, flavors, taste-masking agents, dyes, stabilizers, enzyme inhibitors, and lubricants.

5 The present invention also comprises delivery of the glycopyrrolate compositions to the colon. Because of its location at the distal portion of the alimentary canal, the colon is particular difficult to access. Enteric coatings have been used to bypass absorption in the stomach and deliver the drug to the small intestine. Delivery is based upon the pH differences between these two parts of the alimentary canal. In current techniques for targeting drugs to the colon, solid formulations of the desired drug molecules are coated with a pH-resistant polymeric coating. Such formulations are similar to enteric coated formulations which may be used to deliver drugs to the distal ileum. Enteric coatings include bioerodible polymers such as shellac and cellulose acetate phthalate. Excipients such as triethanolamine myristate can be used for prolongation of GI transit time.

10 In contrast to the enteric coated formulations, however, the formulations for colonic delivery are designed to withstand both low and slightly basic pH values for several hours. During this time, they are assumed to pass the stomach and the small intestine and reach the large intestine, where the coat disintegrates and the drug release process is initiated. The polymers used for this purpose are commonly acrylic acid derivatives or cellulose derivatives such as cellulose acetate phthalate or ethyl cellulose.

25 The present invention comprises methods of administration of glycopyrrolate compositions in transdermal delivery systems for the treatment of sialorrhea, hyperhidrosis, Meniere's Disease and myasthenia gravis. Transdermal methods provide methods of administration that have high patient compliance. The present invention comprises methods of treating Frey's Syndrome or gustatory sweating that include transdermal patches or assisted transdermal delivery such as with electricity or ultrasound.

Transdermal drug delivery (TDD) offers several advantages over traditional delivery methods including injections and oral delivery. When compared to oral delivery, TDD avoids gastrointestinal drug metabolism, reduces first-pass liver metabolism effects, and provides sustained release of glycopyrrolate compositions. In actuality, transdermal delivery is transport of glycopyrrolate compositions across the epidermis where the glycopyrrolate compositions get absorbed in the blood capillaries. When compared to injections, TDD eliminates the associated pain and the possibility of infection. The transdermal route of administration provides an alternative method avoids gastrointestinal degradation and gastrointestinal uptake problems.

One detriment of transdermal delivery of glycopyrrolate compositions is the low permeability of skin. This low permeability is attributed to the stratum corneum, the outermost skin layer which consists of dead cells and keratin fibers, keratinocytes, surrounded by lipid bilayers. The highly ordered structure of the lipid bilayers confers an impermeable character to the skin. The transdermal methods of the present invention include compositions of chemical, permeation or penetration enhancers and methods of applying electricity or ultrasound to enhance transdermal glycopyrrolate composition transport.

Ultrasound has been shown to enhance transdermal transport of drugs (molecular weight less than 500) across human skin, a phenomenon referred to as sonophoresis. It has been shown that application of ultrasound at therapeutic frequencies (1 MHz) induces growth and oscillations of air pockets present in the keratinocytes of the skin in a process known as cavitation. These oscillations disorganize the skin lipid bilayers and enhance transdermal transport.

Transdermal drug delivery offers an advantageous alternative to oral delivery and injections. A variety of delivery systems can be used to enhance transdermal transport of drugs.

These include use of chemicals to either modify the skin structure or to increase the drug concentration in the transdermal patch; applications of electric fields to create transient transport pathways, such as electroporation, or to increase the mobility of charged drugs through the skin, such as in iontophoresis, and application of ultrasound, sonophoresis. U.S. Pat. Nos. 4,309,989 to Fahim and 4,767,402 to Kost, et al, disclose various ways in which ultrasound has been used to achieve transdermal drug delivery.

The present invention contemplates the administration of glycopyrrolate compositions using sonophoresis. Although a variety of ultrasound conditions have been used for sonophoresis, the most commonly used conditions correspond to the therapeutic ultrasound having frequency in the range of 1 MHz- MHz and intensity in the range of 0-2 W/cm<sup>2</sup>. An optimal selection of ultrasound parameters, such as frequency, pulse length, intensity, as well as of nonultrasonic parameters, such as ultrasound coupling medium, can be conducted to ensure a safe and efficacious application using the methods known in the art, such as are taught in U.S. Patent No. 5,814,599, included herein in its entirety. For example, a preferred delivery method of the present invention uses ultrasound at a frequency of between 20 kHz and 10 kHz at an intensity that does not cause irreversible skin damage for a period of time effective to deliver the drug.

As used herein, sonophoresis is the application of ultrasound to the skin on which a glycopyrrolate composition, alone or in combination with a carrier, penetration enhancer, lubricant, or other pharmaceutically acceptable agent for application to the skin, has been applied. Ultrasound is defined as sound at a frequency of between 20 kHz and 10 MHz, with intensities of between greater than 0 and 3 W/cm. As used herein, "low frequency" sonophoresis is ultrasound at a frequency that is less than 1 MHz, more typically in the range of 20 to 40 kHz, which is preferably applied in pulses, for

example, 100 msec pulses every second at intensities in the range of between zero and 1 W/cm<sup>2</sup>, more typically between 12.5 mW/cm<sup>2</sup> and 225 mW/cm<sup>2</sup>. Exposures are typically for between 1 and 10 minutes, but may be shorter and/or pulsed. The intensity should not be so high as to raise the skin temperature more than about one to two degrees Centigrade.

Many ultrasound devices are available commercially which can be used in the present invention. For example, the ultrasonic devices used by dentists to clean teeth have a frequency of between about 25 and 40 kHz. Commercially available portable ultrasound toothbrushes make use of a small sonicator contained within the toothbrush. This sonicator is portable and operates on rechargeable batteries. Small pocket-size sonicators carried by patients and used to "inject" glycopyrrolate compositions whenever required could be readily adapted from these devices.

In summary, the present invention comprises methods of administration of glycopyrrolate compositions for treatment of Frey's Syndrome, gustatory sweating, Meniere's Disease, hyperhidrosis, sialorrhea and myasthenia gravis. Not all administration routes are efficacious for every patient. Therefore, the present invention comprises various methods which require differing formulations of the glycopyrrolate compositions. The formulations include those suitable for oral, rectal, ophthalmic, (including intravitreal or intracameral) nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratracheal, and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by conventional pharmaceutical techniques. Such techniques include the step of bringing into association the active ingredient and the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into associate

the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus, etc.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally coated or scored and may be formulated so as to provide a slow or controlled release of the active ingredient therein.

Formulations suitable for topical administration in the mouth include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the ingredient to be administered in a suitable liquid carrier.

Formulations suitable for topical administration to the skin may be presented as ointments, creams, gels and pastes comprising the ingredient to be administered in a pharmaceutical acceptable carrier. A preferred topical delivery system is a transdermal patch containing the ingredient to be administered.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

5        Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of 20 to 500 microns which is administered in the manner in which snuff is administered, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.  
10        Suitable formulations, wherein the carrier is a liquid, for administration, as for example, a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

15        Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

20        Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be  
25        presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use. Extemporaneous injection solutions and  
30        suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

35        Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the administered ingredient.

5 It should be understood that in addition to the ingredients, particularly mentioned above, the formulations of the present invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include flavoring agents.

10 This invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications, and equivalents thereof which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or the scope of the  
15 appended claims.



## Claims

What is claimed is:

- 5           1.     A method of treatment of a medical condition, wherein the medical condition is selected from the group consisting of Frey's Syndrome, hyperhidrosis, sialorrhea, myasthenia gravis, Meniere's Disease, and gustatory sweating, comprising administering an effective amount of a glycopyrrolate composition.
- 10           2.     The method of Claim 1, wherein the glycopyrrolate composition is administered via oral, nasal, pulmonary, rectal, buccal, vaginal, ocular and transdermal routes.
- 15           3.     The method of Claim 1 wherein the medical condition is hyperhidrosis.
4.     The method of Claim 1 wherein the medical condition is sialorrhea.
- 20           5.     The method of Claim 1 wherein the medical condition is myasthenia gravis.
6.     The method of Claim 1 wherein the medical condition is
- 25     Meniere's Disease.
7.     The method of Claim 1 wherein the medical condition is gustatory sweating.
- 30           8.     The method of Claim 1 wherein the medical condition is Frey's Syndrome.
9.     A method of treatment of a medical condition comprising administering an effective amount of a glycopyrrolate
- 35     composition.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/40526

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/40

US CL :514/424

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/424

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	US 4,885,282 A (THORNFELDT) 05 December 1989 (5/12/89), see column 1, lines 49-54.	1-3, 9 --- 4-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

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18 NOVEMBER 2000

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02 JAN 2001

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer  
*Dorothy Lawrence Fox*  
FREDERICK KRASS

Telephone No. (703) 308-1235